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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/981,583	02/03/1998	ACHIM DICKMANNS	028622/0/0	8241

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EXAMINER
HARRIS, ALANA M

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/22/2002

35

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/981,583	DICKMANNS ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,16-22,29-31,33-35 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12, 16-22, 29-31, 33-35 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Amendment

1. Upon reconsideration the Examiner has withdrawn the finality of the Office action mailed October 22, 2001 as Paper number 25.

2. Claims 1-12, 16-22, 29-31, 33-35 and 38 are pending.

Claims 1-12, 16-22, 29-31, 33-35 and 38 are examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Rejections

Claim Rejections - 35 USC § 103

4. The rejection of claims 1-10, 16-22 and 38 under 35 U.S.C. 103(a) as being unpatentable over Ohnuki et al. (Cancer Research 40:524-534, March 1980), in view of Garcia et al. (Molecular and Cellular Biology 6(6): 1974-1982) and Chang (Biochimica et Biophysica Acta 823:161-194, 1986) is withdrawn in light of Applicants' arguments.

5. The rejection of claims 1-12, 16-22, 29, 30 and 38 under 35 U.S.C. 103(a) as being unpatentable over Ohnuki et al. (Cancer Research 40:524-534, March 1980), in view of Garcia et al. (Molecular and Cellular Biology 6(6): 1974-1982), Blankenstein et

al. (Current Biology 3:694-698, 1991) and Chang (Biochimica et Biophysica Acta 823:161-194, 1986) is withdrawn in light of Applicants' arguments.

6. The rejection of claims 1-10, 16-22, 31 and 38 under 35 U.S.C. 103(a) as being unpatentable over Ohnuki et al. (Cancer Research 40:524-534, March 1980), in view of Garcia et al. (Molecular and Cellular Biology 6(6): 1974-1982), Chang (Biochimica et Biophysica Acta 823:161-194, 1986) and Sigma Cell Culture Catalogue and Price List (1995) is withdrawn in light of Applicants' arguments.

7. The rejection of claims 1-10, 16-22, 33, 34 and 38 under 35 U.S.C. 103(a) as being unpatentable over Ohnuki et al. (Cancer Research 40:524-534, March 1980), in view of Garcia et al. (Molecular and Cellular Biology 6(6): 1974-1982), Chang (Biochimica et Biophysica Acta 823:161-194, 1986) and Gottlinger et al. (Int. J. Cancer 38:47-52, 1986) is withdrawn in light of Applicants' arguments.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

8. Claims 1-10, 16-22 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over ATCC Catalogue, Eighth Edition, page 205, October 1994, in view of Garcia et al. (Molecular and Cellular Biology 6(6): 1974-1982) and Chang (Biochimica et Biophysica Acta 823:161-194, 1986). The catalogue teaches a disseminated non-small cell lung cancer human tumor cell line, specifically NCI-H1155 (ATCC number CRL-

5818). These autologous cells with metastatic potential are derived from a lymph node metastasis, see ATCC product information sheet. The catalogue does not teach the said cell has integrated in its genome or another replicative genetic element the DNA encoding the early region (large T antigen) of non-infectious SV40 DNA in its genome nor at least one additional oncogene. Additionally, the catalogue does not teach that the said cell has integrated in its genome or another replicative genetic element the DNA encoding the early region (large T antigen) of non-infectious SV40 DNA in its genome nor at least one additional oncogene. Additionally, the catalogue does not teach at least one defect in the origin of replication or the *in vitro* process by which the tumor cell incorporates the DNA encoding at least one immortalizing oncogene into a non-immortalized epithelial tumor cell. The ATCC catalogue's product information lacks the method step of incorporating DNA via microinjection, which is performed after the step of carrying out a primary expansion of said epithelial tumor cells comprising the step of culturing in a medium with epidermal growth factor on the extracellular matrix, collagen coated tissue flasks.

However, Garcia does teach an autologous, disseminated immortalized rabbit mammary epithelial tumor cell which has integrated in its genome or another replicative genetic element the DNA encoding the early region (large T antigen) of non-infectious SV40 DNA. The epithelial tumor cell contains at least one defect in the origin of replication. Garcia also teaches an epithelial tumor cell that has integrated in its genome at least one additional oncogene, wherein the additional oncogene is c-Ha-ras. Garcia continues to teach the *in vitro* process by which the tumor cell incorporated the

DNA encoding at least one immortalizing oncogene. The step of incorporating DNA comprising microinjection, which was performed after the step of carrying out a primary expansion of said epithelial tumor cells. The primary expansion comprised the step of culturing in a medium comprising epidermal growth factor on the extracellular matrix, collagen coated tissue flasks. Furthermore, Chang sets forth that microinjection with DNAs, such as SV40 results in the stable transformation of cells to a malignant phenotype, see page 188, column 1, paragraph 2.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the ATCC cell line, CRL-5818 to establish a metastatic cell line suitable for studying the immortalizing and transforming potential of known and candidate genes for epithelial cells. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in the ATCC catalogue, Garcia and Chang that the establishment of such a cell line could be readily made and successfully propagated in order to conduct experiments geared to the long term study of metastasis in many assay systems. Chang states on page 163, column 1, first full paragraph that "[b]esides the obvious use of human epithelial cell *in vitro* to study multistage carcinogenesis...[these] immortalized lines...are invaluable, since they can be used for studying epithelial cell biology, especially differentiation. In addition the lines can used to generate monoclonal antibodies...". Clearly since 1986 "[t]ransformation of mammalian cells in by SV40 is a widely used experimental model for studying viral oncogenesis...", as well as the art known reason to this approach is for scientist to characterize genetic and epigenetic modification that occur during

tumorigenic stages in cells which maintain the phenotypic characteristics of their tissue of origin. Cancer research studies require the use of cells that do not undergo limited proliferation or senescence. These cell lines are quite useful for research on causes, treatment and prevention of cancer.

9. Claims 1-12, 16-22, 29, 30 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over ATCC Catalogue, Eighth Edition, page 205, October 1994, in view of Garcia et al. (Molecular and Cellular Biology 6(6): 1974-1982), Blankenstein et al. (Current Biology 3:694-698, 1991) and Chang (Biochimica et Biophysica Acta 823:161-194, 1986). The teachings of the non-small cell lung cancer cell line, CRL-5818 an epithelial tumor cell lines with metastatic potential, Garcia of methodology to immortalize, incorporate DNA and culturing said cell and Chang have been discussed in the paragraphs above. These references do not teach the epithelial tumor cell having integrated in its genome or another replicative genetic element an externally introduced gene encoding a cytokine immunostimulatory factor, such as interleukin-4 (IL-4).

However, Blankenstein et al. teach the transfer of single cytokine genes into cancer cells. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the claimed invention was made to introduce genes encoding cytokine immunostimulatory factors, such as IL-4, granulocyte colony-stimulating factor and tumor necrosis factor into the non-small cell carcinoma tumor cell of CRL-5818. One of ordinary sill in the art would have been motivated to do so with a reasonable expectation of success by the teachings well known in the art, that the transfer and the

expression of such immunostimulatory factor genes into cancer cells would mediate powerful tumor suppression potential in T-cell deficient animals and appear to be effective even for poorly or non-antigenic tumors. Additionally, Blankenstein et al. report "cancer cells transfected to produce certain cytokines might induce effective tumor-specific immunity in cancer patients".

10. Claims 1-10, 16-22, 31 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over ATCC Catalogue, Eighth Edition, page 205, October 1994, in view of Garcia et al. (Molecular and Cellular Biology 6(6): 1974-1982) and Sigma Cell Culture Catalogue and Price List (1995). The teachings of Carney and Garcia of production of a cultured immortalized metastatic epithelial tumor cell in a medium comprising epidermal growth factor (EGF) have been discussed in the paragraphs above. These references do not teach a medium comprising recombinant human epidermal growth factor (rhEGF) or the basic fibroblast growth factor (bFGF), recombinant human basic fibroblast growth factor (rhbFGF).

However, the Sigma Cell Culture Catalogue teaches the availability of these growth factor supplements at the time the claimed invention was made. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use rhEGF and rhbFGF to supplement the culture medium. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in the ATCC Catalogue of non-small cell lung cancer cell line CRL-5818, Garcia and the Sigma Cell Culture Catalogue to order these

supplements and use them in view of the recommended concentrations and practices listed in the technical section of the catalogue.

11. Claims 1-10, 16-22, 33, 34 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over ATCC Catalogue, Eighth Edition, page 205, October 1994, in view Garcia et al.(Molecular and Cellular Biology 6(6):1974-1982) and Gottlinger et al. (Int. J. Cancer 38:47-53, 1986). The teachings of the non-small cell carcinoma cell line CRL-5818, Garcia and Chang of an immortalized epithelial tumor cell with metastatic potential have been discussed in the paragraphs above. These references do not teach a composition comprising the said epithelial tumor cell, or the said composition comprising a vaccine in combination with a vaccine adjuvant.

However, Gottlinger et al. teach compositions containing epithelial cell surface antigens and *Bordetella pertussis* adjuvant suitable for mounting an immunological response. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to manufacture a composition comprising the epithelial tumor cell of claim 1 in combination with a *B. pertussis* adjuvant. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings of all three references that the production of an adjuvant prepared by culturing autologous epithelial tumor cells coupled with *B. pertussis* adjuvant would be suitable for administration to a non-human animal for augmenting immune responses in order to generate antibodies that would allow one

skilled in the art to biochemically characterize a specific antigen defined by the generated antibodies.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (703) 306-5880. The examiner can normally be reached on 6:30 am to 4:00 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4315 for regular communications and (703) 308-4315 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Alana M. Harris, Ph.D.
November 19, 2002

SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600